



LANGERHANS CELL HISTIOCYTOSIS WITH PULMONARY INVOLVEMENT IN AN INFANT – A CASE REPORT.

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ABSTRACT

Background: Langerhans cell histiocytosis (LCH) is characterized by monoclonal proliferation and infiltration of organs by Langerhans cell. Pulmonary involvement is common in young adults, but it is uncommon in children.

Case summary: A 7 month old female child, presented with shortness of breath and multiple hypopigmented macules with verrucous lesions over scalp. HRCT was chest, showed tiny cysts with cavitary nodules and nodules with reticulations, likely to represent LCH. Skin biopsy had infiltrating epidermis s/o LCH, immunohistochemistry revealed CD1a positive. Hence the diagnosis of Multisystemic Langerhans cell histiocytosis with pulmonary involvement was made. Infant planned to start chemotherapy but deteriorated, and succumbed to the disease.

Conclusion: Pulmonary involvement is generally a component of systemic involvement. Therefore, children with persistent respiratory problems should be carefully evaluated for rare entities like Pulmonary LCH.

KEYWORDS : Langerhans cell histiocytosis, Pulmonary, children, infant

Langerhans cell histiocytosis is a rare clonal disease characterized by the proliferation of CD1a-positive immature dendritic cells.² In newborns and very young infants, it occurs in 1-2 per million.³ Several organ systems are involved including the skin, lymph nodes, brain, lungs, bone, skin, pituitary gland and liver. Lung involvement may occur either in isolation or as a part of multi organ disease. We describe the case of an infant with multisystemic disease with lung involvement, wherein difficulties in diagnosis and advances about pathogenesis are discussed.

CASE

A 7 month old female, presented with shortness of breath since 20 days along with intermittent fever. She had been born at term, birth weight of 2.6 kg, first born of non consanguineous marriage and her growth and development were normal, and immunized for age. There was no history of Koch or significant medical problems in the family. On examination, infant was moderately febrile with heart rate was 130/min, respiratory rate was 72/min, blood pressure was within normal percentile, with good normal volume pulses. Anthropometric evaluation revealed the weight for age <3rd centile, length for age was at 5th centile. She had pallor, no clubbing or cyanosis. The skin on the forehead and preauricular region had seborrheic dermatitis. Respiratory system examination showed minimal subcostal retractions, without any crepitations or wheeze on auscultation. Abdominal examination showed liver was 4 cms, firm with spleen of 3.5 cms. Cardiovascular system and Central nervous system was normal.

Figure 1: Clinical image showing Seborrheic lesions



Investigations revealed hemoglobin of Hb - 4gm/dl, WBC of 7900/mm³, Platelets- 60,000 cumm. Child, requiring two packed red cell transfusions. Peripheral smear revealed microcytic hypochromic anemia with no abnormal cells, platelets were reduced. Alanine transaminase and aspartate transaminase levels were 54 U/L and 62 U/L, respectively. Mantoux test was negative. Chest radiograph showed haziness lower zones bilaterally. At this point, differential diagnosis of Disseminated Koch, Bronchopneumonia with sepsis were thought. Child was started on intravenous Ceftriaxone and Amikacin.

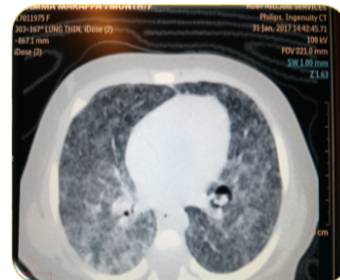


Fig 2: HRCT Chest

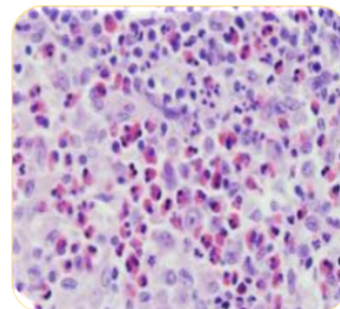


Fig:3 Biopsy of skin Lesions

Later her respiratory distress increased, and developed crepitation. She was given Oxygen through nasal prongs. She had petechiae over the chest. The gastric lavage for CBNAAT

did not detect tuberculosis. Meanwhile we requested for skin biopsy keeping in mind, differential of Langerhans Cell Histiocytosis. High Resonance Computerised Tomography (HRCT) of chest which showed tiny cysts with cavitatory nodules and nodules with reticulations likely to represent LCH. Skin biopsy was reported as Cells with pale nuclei showing folding and grooves, infiltrating epidermis s/o LCH and Immunohistochemistry revealed CD1a positive. Thus, the diagnosis of Multisystemic LCH with Pulmonary involvement was made. The patient was started on oral prednisolone and planned weekly intravenous vinblastine as per LCH treatment protocol. But there was clinical deterioration with worsening cough, breathlessness, child required mechanical ventilated and eventually succumbed.

DISCUSSION:

"Langerhans cell histiocytosis" (LCH) involves a spectrum of clinical presentations ranging from a single bone lesion or trivial skin rash to an explosive disseminated disease.⁵ blood Langerhans cell histiocytosis in children is rare with incidence that ranges between 2.6 to 8.9 cases per million per year.⁴ Peak age at diagnosis is 2 years among children less than 15 years. LCH was first described around 1900 with reports of children with skin lesions, lytic bone lesions, and diabetes insipidus (DI), classified as Hand-Schüller-Christian disease.⁵ The Lichtenstein noted that it associated with histiocytes [1] in 1953 and given named "histiocytosis X". In the 1970s, Nezelof discovered the specific marker of Langerhan cells, Birbeck granules, a cytoplasmic rod or tennis racket shaped organelle, ultimately associated with langerin (CD207), in the lesional LCH cells. The disease has since been named "Langerhans cell histiocytosis."⁷ LCs express CD1a molecules at exceptionally high levels along with another membrane-associated C-type lectin, Langerin(CD207).⁸

A breakthrough in understanding of LCH pathogenesis came with the discovery of *BRAF-V600E* mutations in over 50% of LCH lesions.⁵ (BRAF gene encodes for B-raf Protein) Another common mutation emerging is MAP2K1 (Mitogen activated protein kinase 1, is a protein kinase that is a known downstream target of RAF and is upstream of ERK) seen in 10 to 20% of patients. According to this model, the stage of differentiation in which pathologic ERK (Extracellular Signal-Regulated Kinase) activation arises, following these mutations, determines the clinical manifestations of LCH.⁵ It suggests that, activating mutations in hematopoietic stem cells or undifferentiated myeloid DC precursors result in multifocal high-risk disease, whereas mutations in tissue-restricted precursors results in multifocal low-risk disease, and mutations in more differentiated tissue-restricted precursor cells result in a single lesion.⁵

LCH, is however, believed to be under-diagnosed, since some patients may have only some manifestations, while others have symptoms that are mistaken for infection or other conditions. This makes diagnosis of LCH, a challenging one and also delays it. It may appear as a single lesion or can affect many body systems, such as skin, bone, lymph glands, liver, lung, spleen, brain, pituitary gland and bone marrow. Information has been collected in various studies which show that bone involvement occurs in approximately 78% of patients with LCH and often includes the skull (49%), hip/pelvic bone (23%), upper leg bone (17%) and ribs (8%). Skin LCH is seen in as many as 50% of patients.² Lung lesions are seen in 20% to 25% of patients, while 30% of patients have lymph node involvement.² In a study, about half of children with Pulmonary LCH were asymptomatic, and the prognosis depended on the presence or absence of other risk-organ involvement.¹⁰

It is usually diagnosed with a tissue **biopsy**, in addition to other testing, such as. A biopsy of an involved site is necessary to

make a definitive diagnosis showing abnormal clusters of CD1a⁺/CD207⁺ histiocyte, with Immunocytochemistry positive for S100 and CD1A stain. The extent of the disease needs to be defined for optimal intensity and of duration of chemotherapy. Investigations x-rays and blood studies, ultrasonography/MRI for suspected liver involvement is required. MRI for pulmonary lesions, brain and bone marrow biopsy and aspirate may be required on patients younger than 2 years old or any patients with cytopenias.^{3,5} Positron emission tomography-computed tomography (PET-CT) helps in assessing extent of involvement pre and post chemotherapy

Patients with lesions in "risk organs" including bone marrow, spleen, or liver have significantly higher risk of mortality than patients with lesions limited to "nonrisk" sites. Low risk, initially treat patients with symptomatic lesions with oral weekly methotrexate and 6-mercaptopurine, then adjust as needed for myelosuppression. Patients with deep ulcerative LCH lesions who do not respond to oral therapy may require systemic chemotherapy.⁵ The current standard of care for patients with high-risk LCH is 1 year of therapy with vinblastine/prednisone/mercaptopurine, based on the LCH-III study. Targeted inhibition of MAPK activation is an emerging therapeutic strategy for LCH, more research studies and clinical trials need to evaluate this.

This case highlights the need for high index of suspicion for the LCH in children presenting with respiratory symptoms. Rapid progression of the disease, as in the current case, points towards the need for prompt diagnosis, as the morbidity and prognosis is highly related on the extent of organ involvement.

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